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EXAMINER	
HAQ, SHAFIQUL	
ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
04/21/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/790,746	ARMBRUSTER ET AL.	
	Examiner	Art Unit	
	SHAFIQUL HAQ	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16 and 19-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16 and 19-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

1. Claims 1-15 and 17-18 have been canceled and new claims 19-28 have been added by Applicants and thus claims 16 and 19-28 remain in the case.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 16 and 19-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
4. Claim 16 recites “adding an amount of the measurement sample to a sample of the antibody” in lines 8-9. The recitation “a sample of the antibody” is confusing as to what is intended by “a sample" of the antibody.
5. Claim 16 as claimed discloses two different structures with the same formula (I). It is vague and indefinite as to what structure is intended for the vitamin D derivative of formula (I) in the method step.
6. Claim 19 recites “wherein said competitive binding assay is selected from the .....". Claim 19 is dependent on claim 16 and claim 16 three steps in the method process and it is unclear which step(s) in the method of claim 16 is intended to describe by the phrase “competitive binding assay is selected from the ……”. Moreover, step i), ii) or iii) does not recite the term “competitive binding assay”.

7. Claim 20 recites “wherein the method is a sandwich immunoassay .....". Claim 20 is dependent on claim 16 and claim 16 three steps in the method process and it is unclear which step(s) in the method of claim 16 is intended to describe by the phrase “wherein the method is a sandwich immunoassay ……”

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 16 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 16 recites "separating 25-hydroxy vitamin D from 1α,25-dihydroxy vitamin D by binding 1α,25-dihydroxy vitamin D in a sample of the human serum to a material that specifically binds 1α,25-hydroxy vitamin D and eluting 1α,25-dihydroxy vitamin D from said material to provide a measurement sample”.

The phrase “material that specifically binds 1α,25-hydroxy vitamin D” encompasses any material (e.g. microtiter plate having immobilized anti-1α,25-dihydroxy vitamin D antibody, beads or microparticles having immobilized vitamin D binding protein or anti-1α,25-dihydroxy vitamin D antibody) that specifically binds to 1α,25-dihydroxy vitamin D. However, in the specification, the scope of the “material” and the description for the material for separating 25-hydroxy vitamin D from 1α,25-

dihydroxy vitamin D is strictly limited to successive purification using adsorption chromatography, as for example, Exrelut Kieselguhr columns and then with silica columns, which is structurally and functionally distinct from the purification materials as encompassed by the phrase as described above.

The MPEP states that the purpose of written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject mater later claimed and the specification does not have clear written descriptive support for separating 25-hydroxy vitamin D from 1α,25-dihydroxy vitamin D with all binding materials as encompassed by the amended claims.

Accordingly, it is deemed that the specification fails to provide adequate written description and clear guidance for all the materials that specifically binds 1α,25-dihydroxy vitamin D as encompassed by the claim and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 16, 19-25 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deluka *et al* (EP 0583945 A2) in view of Mawer *et al* (1985, admitted prior art: see page 33, lines 25-27 of the specification) and Holick et al. (WO 97/24127).

Deluca teaches a method of measuring 1α,25-dihydroxy vitamin D in a sample. The method involves extracting 1α,25-dihydroxy vitamin D from a sample by separation out other vitamin D metabolites using silica to provides a measurement sample containing 1α,25-dihydroxy vitamin D and then detecting 1α,25-dihydroxy vitamin D in the measurement sample using competitive binding assay by displacement of labeled 1α,25-dihydroxy vitamin D derivative from a receptor protein that specifically binds to 1α,25-dihydroxy vitamin D in the presence of the measurement sample and detecting the bound receptor with a labeled antibody binding to the receptor (see abstract, col.7, lines 30-33 and claim 1).

Deluca disclose receptor protein that specifically binds 1α,25-dihydroxy vitamin D but does not teach anti-1α,25-dihydroxy vitamin D antibody as receptor protein. Deluca disclose radiolabeled 1α,25-dihydroxy vitamin D as a competitor (tracer) but does not teach using non radioactive biotin labeled 1α,25-dihydroxy vitamin D as a tracer.

Mawer discloses monoclonal mouse anti-1α,25-dihydroxy vitamin D antibody specifically binding to 1α,25-dihydroxy vitamin D (see page 33, lines 25-26 of the specification).

Holick teaches methods for detecting the presence of vitamin D analogs and their metabolites in a sample using labeled vitamin D compounds (e.g. detectable biotin

labeled vitamin D derivative) in the assay method (see field of invention). The vitamin D metabolite include 1,25 dihydroxy vitamin D3 (page 5, lines 14 and 17-18) and compounds B, C and G (see compounds B and C of example 2 and 3 of pages 14-15 and Fig. 6 for compound G) are disclosed by Holick as non-radioactive tracers for use in a competitive immunoassay (page 10, lines 21-24; page 22, lines 7-13) and the tracers are obvious over the compound of the formula of claim 1 when R represents a 25-hydroxy side-group of vitamin D3 and Y=hydroxyl. Holick teaches that nonradioactive detection of 1,25(OH)2D is highly desirable (page 5, lines 17-18) because radioisotopes are very costly, hazardous to handle and store and radioactive disposal is becoming an extremely costly affair (page 4, lines 5-7). Holick discloses a method in which labeled vitamin D derivative is first allowed to bind to an antibody capable of binding to the vitamin D derivative which is attached to a solid support. Sample containing vitamin D metabolite is then added to effect displacement of the labeled compound from said antibody (see pages 11-12). Holick discloses different immunoassay methods (page 10, lines 21-25 and page 12, lines 9-11) and solid phase support including dextran, agarose, polystyrene and microtitration plate (page 11, lines 27-29) and the solid phase can be beads, plates or tubes (page 10, lines 15-16). Holick *et al* further teach that any antibody which is capable of binding vitamin D, its metabolite or analog can be used (page 12, lines 5-6).

Therefore, with the foregoing description in mind one of ordinary skill in the art would have found it obvious to modify Deluka's method by substituting the

monoclonal anti-1α,25-dihydroxy vitamin D antibody that specifically binds to 1α,25-dihydroxy vitamin D (Mawer *et al*) for the receptor protein with the expectation of improving sensitivity of detection with increase specificity because monoclonal antibody is considered to have high specificity for a given hapten. Further, with this substitution in mind, the skilled artisan would also consider substituting the radioactive tracer of Deluka with the non-radioactive tracer of Holick because Holick teaches that nonradioactive detection of $1,25(OH)_2D$ is highly desirable (page 5, lines 17-18) as radioactive tracer involves radioisotopes that are very costly, hazardous to handle and store and radioactive disposal is becoming an extremely costly affair (page 4, lines 5-7). Moreover, Holick teaches that the labeled compounds may be used in any conventional assay for vitamin D compounds such as competitive binding assays (page 10, lines 21-24). Further, with regard to correlation with standards, Holick teaches assay with standard samples (see page 22) and correlation of results from sample with results from known standards are well known in the field of immunoassay detection and would be considered to be obvious absent unexpected results.

With regard to kit claims 19-24 and 28, Deluca teaches compiling immunoiassay components in a kit (see claim 8) and since the packaging of components in a kit form is a well-known obvious expedient for ease and convenience in assay performance, once a method has been established, one skilled in the art would clearly consider compiling in a kit format and change/modify different components of the kit to best suit the assay.

With regard to claims 25-26, Deluca does not teach various solid phase based immunoassay detection of the extracted 1α,25-dihydroxy vitamin D but different variations of known immunoassay detections including different variations of known solid support based detections as described by Holick (page 10, lines 21-29; page 11, lines 27-29) for the detection of the extracted 1α,25-dihydroxy vitamin D with the anti-1α,25-dihydroxy vitamin D antibody and the biotin labeled tracer would be obvious to one of ordinary skill in the art and as described above, the components for the particular immunoassays in a kit would also be obvious to one of ordinary skill in the art. Note that as evidenced from the claimed broad detection methods and broad use of solid phase (see claims 19-20 and 23-23), a particular detection methods or a particular sold phase has not been described as being critical to the practice of the invention and thus

12. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Deluka *et al* (EP 0583945 A2) in view of Mawer *et al* (1985, admitted prior art: see page 33, lines 25-27 of the specification) and Holick et al. (WO 97/24127) as described above and further in view of DeLuca et al. (US 5,064,770).

See above teaching of Deluka in view of Mawer and Holick for the obviousness of the various immunoassay detection of the extracted 1α,25-dihydroxy vitamin D in the sample.

Holick discloses kit comprising solid phase (e.g. beads) and vitamin D derivative but differ from the instant application in failing to disclose magnetic microparticle as solid phase.

DeLuca et al. in a binding assay to determine 1, 25-dihydroxy vitamin D receptor disclose using magnetic particle for anchoring binding molecules to the particle.

Since the use of magnetic particle is very common in the field of immunoassay and magnetic particle has been disclosed for detection of vitamin D binding protein (DeLuca et al.), it would be obvious to one of ordinary skill in the art at the time the invention is made consider magnetic particle in the solid phase based detection of 1α,25-dihydroxy vitamin D as described above by combined teaching of the references.

Response to Argument

13. Applicant's arguments and amendments filed 4/11/2011 have been fully considered and are persuasive to overcome rejections of 11/10/2010 but however, Applicant's arguments have been rendered moot in view of the new grounds of rejections as described in this office action necessitated by Applicant's amendments.

Conclusion

14. Applicants' amendment necessitated new ground(s) of rejection presented in this office action. Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and

any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicant should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (e.g., if the amendment is not supported in ipsis verbis, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shafiqul Haq whose telephone number is 571-272-6103. The examiner can normally be reached on 7:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shafiqul Haq/
Primary Examiner, Art Unit 1641